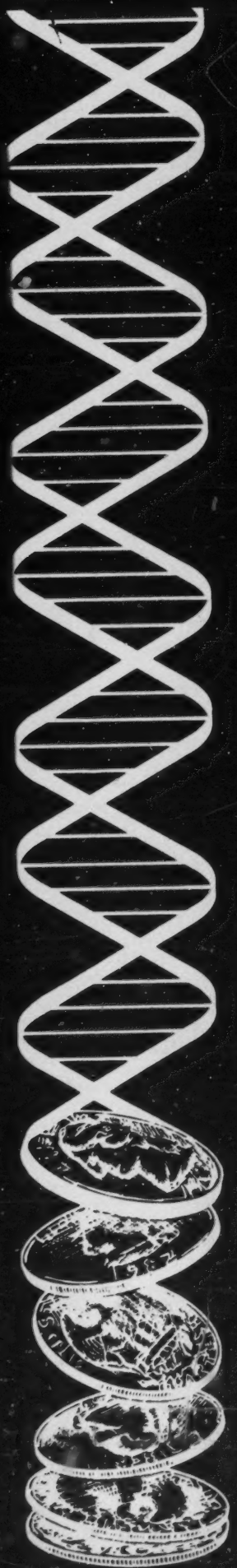

COMMERCIAL BIOTECHNOLOGY

An International Analysis

Summary

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Washington, D.C. 20510

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The Technology Assessment Board approves the release of this report. The views expressed in this report are not necessarily those of the Board, OTA Advisory Council, or of individual members thereof.

Foreword

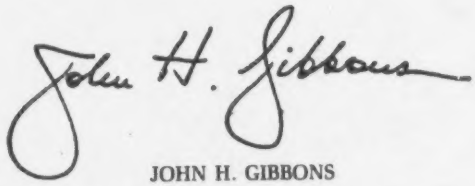
This report assessing the competitive position of the United States with respect to Japan and four European countries believed to be the major competitors in the commercial development of "new biotechnology" continues a series of OTA studies on the competitiveness of U.S. industries. It was requested by the House Committee on Science and Technology and the Senate Committee on Commerce, Science, and Transportation. Additionally, a letter of support for this study was received from the Senate Committee on Labor and Human Resources.

New biotechnology, defined in this report as the industrial use of recombinant DNA, cell fusion, and novel bioprocessing techniques, has potential applications in pharmaceuticals, plant and animal agriculture, specialty chemicals and food additives, environmental applications, commodity chemicals and energy production, and bioelectronics. In the past several years, over 100 new firms have been started in the United States to capitalize on the commercial potential of biotechnology, and large established companies in the United States, Japan, and Europe have invested in this technology.

A well-developed life science base, the availability of financing for high-risk ventures, and an entrepreneurial spirit have led the United States to the forefront in the commercialization of new biotechnology, but continuation of the initial preeminence of American companies in this field is not assured. Japan is likely to be the leading competitor of the United States, followed by the Federal Republic of Germany, the United Kingdom, Switzerland, and France.

Congressional policy options for improving U.S. competitiveness in biotechnology are identified in this report. The options pertain to Federal funding for the basic life sciences and for generic applied research, especially in the areas of bioprocess engineering and applied microbiology (including the training of personnel in these areas), financing for small entrepreneurial new biotechnology firms, and clarification and modification of particular aspects of intellectual property law, health, safety, and environmental regulation, antitrust law, and export control laws.

OTA was assisted in the preparation of this study by an advisory panel of individuals representing a wide range of backgrounds, including science, economics, financial analysis, law, labor, and new and established firms commercializing biotechnology. Additionally, over 250 reviewers from universities, the private sector, and government agencies, both domestic and foreign, provided helpful comments on draft reports. OTA expresses sincere appreciation to each of these individuals. As with all OTA reports, however, the content is the responsibility of the Office and does not necessarily constitute the consensus or endorsement of the advisory panel or the Technology Assessment Board.



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Commercial Biotechnology: An International Analysis

Introduction

In the past 10 years, dramatic new developments in the ability to select and manipulate genetic material have sparked unprecedented interest in the industrial uses of living organisms. Following the first successful directed insertion of foreign DNA in a host micro-organism in 1973, scientific researchers in the United States and other countries began to recognize the potential for directing the cellular machinery to develop new and improved products and processes in a wide diversity of industrial sectors. Potential industrial applications of novel genetic techniques include the production of new drugs, food, and chemicals, the degradation of toxic wastes, and the improvement of agricultural products. Thus, these new techniques could have a major economic impact on industries throughout the world.

Beginning around 1976, many small entrepreneurial firms were formed in the United States specifically to build on the growing body of fundamental knowledge in molecular biology and to exploit it to a profitable end. Furthermore, large established American, Japanese, and European companies in a broad spectrum of industrial sectors expanded their research and development (R&D) programs to include the new genetic techniques. In the United States, private sector investments to commercialize these new techniques exceeded $1 billion in 1983.

This report assesses the competitive position of the United States with respect to Japan and four European countries—the Federal Republic of Germany, the United Kingdom, Switzerland, and France—believed to be the major competitors in the commercial development of "new biotechnology," as defined below. **Although the United States is currently the world leader in both basic science and commercial development of new biotechnology, continuation of the initial preeminence of American companies in the commercialization of new biotechnology is not assured.** Japan and other countries have identified new biotechnology as a promising area for economic growth and have therefore invested quite heavily in R&D in this field. Congressional policy options for improving U.S. competitiveness in new biotechnology are identified in this report.

Definitions

Biotechnology, broadly defined, includes any technique that uses living organisms (or parts of organisms) to make or modify products, to improve plants or animals, or to develop micro-organisms for specific uses. Biological processes and organisms have been used with great success throughout

history and have become increasingly sophisticated over the years. Since the dawn of civilization, people have deliberately selected organisms that improved agriculture, animal husbandry, baking, and brewing. More recently, a better understanding of genetics has led to more effective applications of traditional genetics in such areas as antibiotic and chemical production.

This report focuses on the industrial use of recombinant DNA (rDNA), cell fusion, and novel bioprocessing techniques. To differentiate between biotechnology using these novel techniques and the more traditional forms of biotechnology, this report uses the terms "new biotechnology" and "old biotechnology," respectively. Thus, for example, traditional wine production is old biotechnology, but the use of yeast modified with rDNA techniques to produce wine with a higher alcohol content is new biotechnology. Where no specific distinction is made, the term biotechnology alone henceforth refers to new biotechnology.

Biotechnology is the most recent phase in a historical continuum of the use of biological organisms for practical purposes. Furthermore, developments arising from existing technologies are providing a base from which other technologies will emerge, and new technologies can make even the most potentially useful current technology obsolete in a short time. Of necessity, this assessment describes the development of biotechnology at a particular point in time, but it is important to emphasize that dynamic and progressive change has characterized biotechnology for the last decade. Figure 1 shows some prominent events that illustrate the rapid progress made in the development of biotechnology over the last decade. This pace is likely to continue into the 21st century.

The technologies

The novel techniques used in biotechnology are extremely powerful because they allow a large amount of control over biological systems. *Recombinant DNA technology,* one of the new techniques, can be used in a wide range of industrial sectors to develop micro-organisms that produce new products, existing products more efficiently, or large quantities of otherwise scarce products. This technology can also be used to develop organisms that themselves are useful, such as micro-organisms that degrade toxic wastes or new strains of agriculturally important plants.

Cell fusion, the artificial joining of cells, combines the desirable characteristics of different types of cells into one cell. This technique has been used recently to fuse certain cancer cells and specialized cells of the immune system to produce a cell line known as a hybridoma which produces large quantities of *monoclonal antibodies (MAbs).* MAbs can be used in the diagnosis and treatment of disease and the purification of proteins.

Bioprocess technology, though not a novel genetic technique, allows the adaptation of biological methods of production to large-scale industrial use. **In the next decade, competitive advantage in areas related to biotechnology may depend as much on developments in bioprocess engineering as on innovations in genetics, immunology, and other areas of basic science.**

Figure 1.—Major Events in the Commercialization of Biotechnology

1973	First gene cloned.
1974	First expression of a gene cloned from a different species in bacteria. Recombinant DNA (rDNA) experiments first discussed in a public forum (Gordon Conference).
1975	U.S. guidelines for rDNA research outlined (Asilomar Conference). First hybridoma created.
1976	First firm to exploit rDNA technology founded in the United States (Genentech). Genetic Manipulation Advisory Group (U.K.) started in the United Kingdom.
1980	*Diamond* v. *Chakrabarty*—U.S. Supreme Court rules that micro-organisms can be patented under existing law. Cohen/Boyer patent issued on the technique for the construction of rDNA. United Kingdom targets biotechnology (Spinks' report). Federal Republic of Germany targets biotechnology (Leistungsplan). Initial public offering by Genentech sets Wall Street record for fastest price per share increase ($35 to $89 in 20 minutes).
1981	First monoclonal antibody diagnostic kits approved for use in the United States. First automated gene synthesizer marketed. Japan targets biotechnology (Ministry of International Trade and Technology declares 1981 "The Year of Biotechnology"). France targets biotechnology (Pelissolo report). Hoescht/Massachusetts General Hospital agreement. Initial public offering by Cetus sets Wall Street record for the largest amount of money raised in an initial public offering ($125 million). Industrial Biotechnology Association founded. DuPont commits $120 million for life sciences R&D. Over 80 NBFs had been formed by the end of the year.
1982	First rDNA animal vaccine (for colibacillosis) approved for use in Europe. First rDNA pharmaceutical product (human insulin) approved for use in the United States and the United Kingdom. First R&D limited partnership formed for the funding of clinical trials.
1983	First plant gene expressed in a plant of a different species. $500 million raised in U.S. public markets by NBFs.

SOURCE: Office of Technology Assessment.

Industrial development

The industrial sector in which the earliest applications of new biotechnology have occurred is the pharmaceutical sector. Reasons for the rapid diffusion of the new techniques into the pharmaceutical sector include the following:

- Recombinant DNA and MAb technologies were developed with public funds directed toward biomedical research. The first biotechnology products, such as rDNA-produced human insulin, interferon, and MAb diagnostic kits, are a direct result of the biomedical nature of the basic research that led to these new technologies.
- Pharmaceutical companies have had years of experience with biological production methods, and this experience has enabled them to take advantage of the new technologies.
- Pharmaceutical products are high value-added and can be priced to recover costs incurred during R&D, so the pharmaceutical sector is a good place to begin the costly process of developing a new technology.

Because the pharmaceutical sector is currently most active in commercializing biotechnology, it serves as a model for the industrial development of biotechnology in much of this report. It is important to recognize, however, that the development of biotechnology in other industrial sectors will differ from its development in the pharmaceutical sector. Regulatory and trade barriers and a marketing and distribution system unique to the pharmaceutical sector, for example, limit its usefulness as a model.

Findings

Industrial applications of biotechnology

Industrial applications of biotechnology will be found in several industrial sectors, including pharmaceuticals, animal and plant agriculture, specialty chemicals and food additives, environmental areas, commodity chemicals and energy production, and bioelectronics.

The earliest industrial applications of biotechnology (i.e., during the next 5 to 10 years) are likely to occur in pharmaceuticals, animal agriculture, and specialty chemicals. Applications of biotechnology to **pharmaceuticals** being pursued at present are in the production of proteins such as insulin, interferon, and human serum albumin; antibiotics; MAb diagnostics; and vaccines for viral, bacterial, and parasitic diseases. As more is learned about hormone growth factors, immune regulators, and neurological peptides, their importance in the treatment of disease may increase dramatically. Eventually, the production of such regulatory proteins may turn out to be the largest application of biotechnology in the pharmaceutical industry.

In **animal agriculture,** biotechnology is being used to develop products similar to those being developed in the pharmaceutical industry. However, since animal producers cannot afford to purchase expensive products made with new technology, biotechnologically produced products may initially be limited to products for "high value" animals such as pets and breeding

stock. The most important products are likely to be vaccines and growth promotants.

The production of **specialty chemicals** (i.e., chemicals costing more than $1/lb) and **food additives*** represents one of the largest opportunities for the application of biotechnology because of the diversity of potential applications. Biotechnology could potentially be used to improve existing bioprocesses such as those used in the production of amino acids. In the production of products such as vitamins and steroid compounds, which are currently made in multistep production processes involving chemical syntheses, biotechnology could provide one or more enzymatic conversion processes to increase the specificity of currently used chemical conversions. Generally, complex products, such as enzymes and some polysaccharides, can only be made economically using bioprocesses. Several companies in the United States are pursuing biological production of specialty chemicals, but most specialty chemicals currently produced biologically are made almost exclusively in Japan and Europe, and these countries intend to pursue new applications for specialty chemical production.

Applications of rDNA technology to **plant agriculture** are proceeding faster than anyone anticipated 3 to 4 years ago. Some important traits of plants, including stress-, herbicide-, and pest-resistances, appear to be rather simple genetically, and it may be possible to transfer these traits to important crop species in the next few years. Other traits, such as increased growth rate, increased photosynthetic ability, and the stimulation of nitrogen fixation, are genetically complex, and it is likely to be several years before plants with these characteristics developed with rDNA technology will be ready for field testing. Micro-organisms that interact with plants offer possibilities for genetic manipulation that may be more near-term. For instance, it may be possible to manipulate micro-organisms to produce pesticides or inhibit frost formation.

Environmental applications of biotechnology include mineral leaching and metal concentration, pollution control and toxic waste degradation, and enhanced oil recovery. These applications may take longer to reach the market, because little is known of the genetics of the most potentially useful micro-organisms. Additionally, regulation is expected to be a major factor influencing development of this area, because these applications use micro-organisms that are deliberately released into the environment. The nature and extent of this regulation remains uncertain, and this uncertainty may deter some firms from entering the field, thus slowing development.

Commodity chemicals now produced from petroleum feedstocks could be produced biologically from biomass feedstocks such as cornstarch and lignocellulose. Commodity chemical production from cornstarch will probably occur before production from lignocellulose because of the high energy inputs necessary for the solubilization of lignocellulose. Although the technology exists now for the cost-effective biological production of some commodity chemicals such as ethanol, the complex infrastructure of the com-

*Food additives are considered together with specialty chemicals because many (though not all) food additives are also specialty chemicals, e.g., amino acids and vitamins.

modity chemical industry will probably prevent the replacement of a large amount of commodity chemical production using biotechnology for at least 20 years. This distant time horizon is due more to the integrated structure of the chemical industry, its reliance on petroleum feedstocks, and its low profit margins than to technical problems in the application of the biotechnology.

In the area of **bioelectronics,** biotechnology could be used to develop improved biosensors or new conducting devices called biochips. Sensors that use enzymes for detecting specific substances are available now. However, their use is limited by the narrow range of substances they detect and by their temperature instability. Biotechnology could be instrumental in the development of more versatile sensors that use enzymes or MAbs. Better sensors would be especially useful in the control of industrial bioprocesses. Biotechnology may also make it possible to construct devices that use proteins as a framework for molecules that act as semiconductors. The anticipated advantages of these biochips are their small size, reliability, and the potential for self assembly. The production of biochips, however, is one of the most distant applications of biotechnology.

The U.S. competitive position

A well-developed life science base, the availability of financing for high-risk ventures, and an entrepreneurial spirit have led the United States to the forefront in the commercialization of biotechnology. For the most part, the laws and policies of this country have made it possible for industrialists and scientists to capitalize rapidly on the results of basic research in biotechnology conducted in the university system and government laboratories. The relative freedom of U.S. industry to pursue a variety of courses in the development of products has also given the United States a comparative advantage. The flexibility of the U.S. industrial system and the plurality of approaches taken by entrepreneurial new biotechnology firms (NBFs) and established companies in the development of products have facilitated the rapid development of biotechnology in the United States.

Japan is likely to be the leading competitor of the United States for two reasons. First, Japanese companies in a broad range of industrial sectors have extensive experience in bioprocess technology. Japan does not have superior bioprocess technology, but it does have relatively more industrial experience using old biotechnology, more established bioprocessing plants, and more bioprocess engineers than the United States. Second, the Japanese Government has targeted biotechnology as a key technology of the future, is funding its commercial development, and is coordinating interactions among representatives from industry, universities, and government. **The United States may compete very favorably with Japan if it can direct more attention to research problems associated with the scaling-up of bioprocesses for production.**

The European countries are not moving as rapidly toward commercialization of biotechnology as either the United States or Japan, in part because the large established pharmaceutical and chemical companies in

Europe have hesitated to invest in biotechnology and in part because of cultural and legal traditions that tend not to promote venture capital formation and, consequently, risk-taking ventures. Nevertheless, several of the large pharmaceutical and chemical companies in the United Kingdom, the Federal Republic of Germany, Switzerland, and France will surely be competitors in selected product areas in the future because of their prominent position in world sales of biologically derived products. Additionally, the increased interest shown recently by the British Government in biotechnology may speed its development in the United Kingdom.

The United States could have difficulty maintaining its competitive position in the future if several issues are not addressed. If U.S. Government funding for basic life science research continues its decline, the science base, which is the source of innovation in biotechnology as well as in other fields, may be eroded. U.S. Government funding of generic applied research,* especially in the areas of bioprocess engineering and applied microbiology, is currently insufficient to support rapid commercialization. U.S. Government funding for personnel training in these areas may also be insufficient. Additionally, clarification and modification of certain aspects of U.S. health, safety, and environmental regulation and intellectual property law may be necessary for the maintenance of a strong U.S. competitive position in biotechnology.

Analysis of international competitiveness in biotechnology

As of the end of 1983, only a few products of new biotechnology had reached the marketplace—notably human insulin, some MAb diagnostic kits, and some animal vaccines. Since the technologies are still emerging and most biotechnology products and processes are in early development, traditional parameters of international competitiveness are difficult or impossible to estimate. Instead of examining the classical measures of competitiveness, therefore, OTA's analysis of international competitiveness in biotechnology examines the aggregate industrial activity in biotechnology in both domestic and foreign firms and 10 factors that might be influential in determining the competitive position of the United States and other countries with respect to the commercialization of biotechnology. The following five countries were identified as the likely major competitors of the United States in the commercialization of biotechnology: Japan, the Federal Republic of Germany, the United Kingdom, Switzerland, and France. Although companies from many countries will have biotechnology products in world markets, these five countries were selected because of their research capabilities in biology and their existing capabilities in old biotechnology and because, as a whole, their companies are most likely to reach world markets first with biotechnology-produced products.

*Generic applied research, which is nonproprietary and bridges the gap between basic research and aplied research, is aimed at the solution of generic problems that are associated with the use of a technology by industry.

OTA's industrial analysis was approached from three perspectives:

- the number and kinds of companies commercializing biotechnology,
- the markets targeted by industrial biotechnology R&D, and
- the interrelationships among companies applying biotechnology and the overall organization of the commercial effort.

Ten factors were identified as potentially important in determining the future position of the United States and other countries in the commercialization of biotechnology:

- financing and tax incentives for firms;
- government funding of basic and applied research;
- personnel availability and training;
- health, safety, and environmental regulation;
- intellectual property law;
- university/industry relationships;
- antitrust law;
- international technology transfer, investment, and trade;
- government targeting policies in biotechnology; and
- public perception.

The relative importance of each of the factors to competitiveness today is shown in figure 2. Some factors could become more important as the technology matures and more products reach the marketplace.

OTA's principal findings with respect to the types and activities of firms commercializing biotechnology, the factors potentially important to international competitiveness in biotechnology, and other considerations such as historical patterns of industrial commercialization, the lack or abundance of particular natural resources, and the tendency toward risk taking in each country are presented below.

Overview of U.S. and foreign companies commercializing biotechnology

U.S. and foreign efforts to develop and commercialize biotechnology differ substantially in character and structure. In the United States, two distinct sets of firms are pursuing commercial applications of biotechnology—NBFs and established companies. NBFs are entrepreneurial ventures founded specifically to commercialize innovations in biotechnology. The established companies are generally process-oriented, multiproduct companies in traditional industrial sectors such as pharmaceuticals, energy, chemicals, and food processing. Figure 3 illustrates the percentage of U.S. firms pursuing biotechnology R&D in specific application areas.

U.S. efforts to commercialize biotechnology are currently the strongest in the world. The strength of U.S. efforts is in part derived from the unique complementarity and competition that exist between NBFs and established U.S. companies in developing biotechnology for wider commercial application. At present, most NBFs are still specializing in research-oriented phases of development, precisely the commercial stage where they excel. Through their R&D efforts, NBFs are contributing to innovation, ex-

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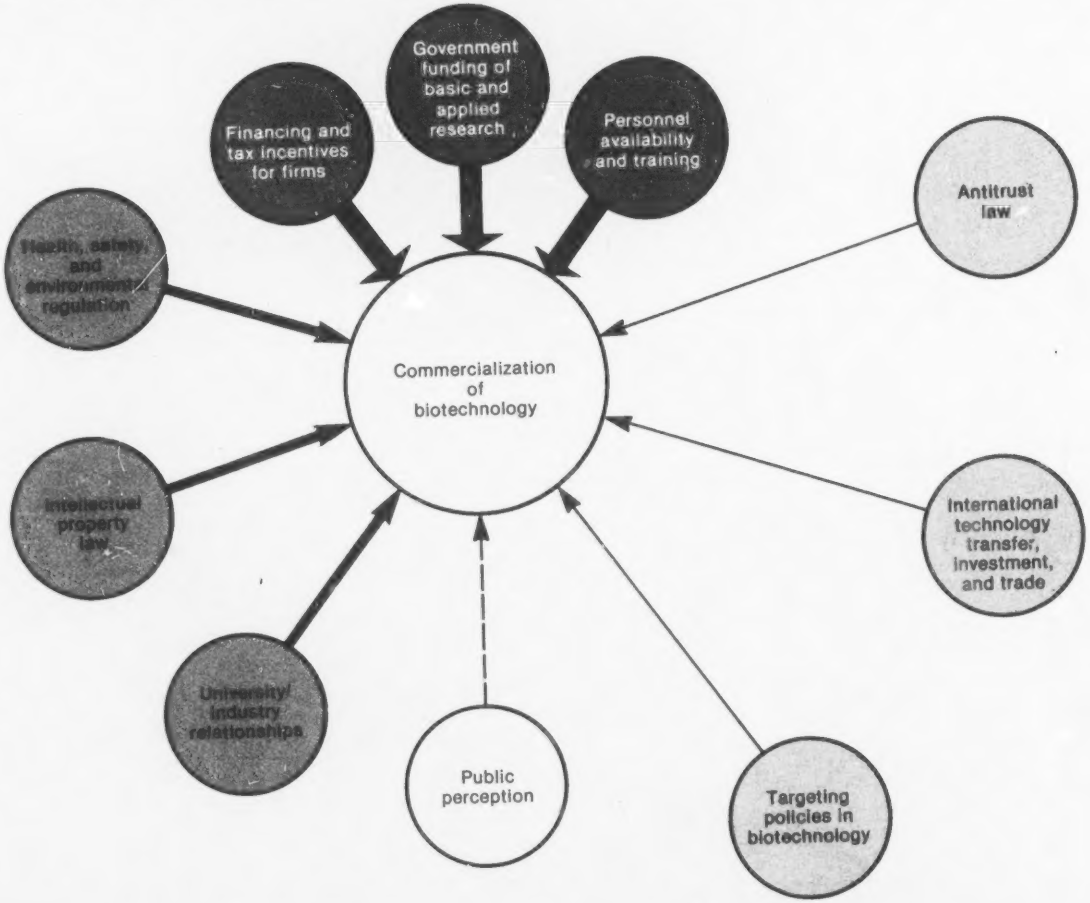
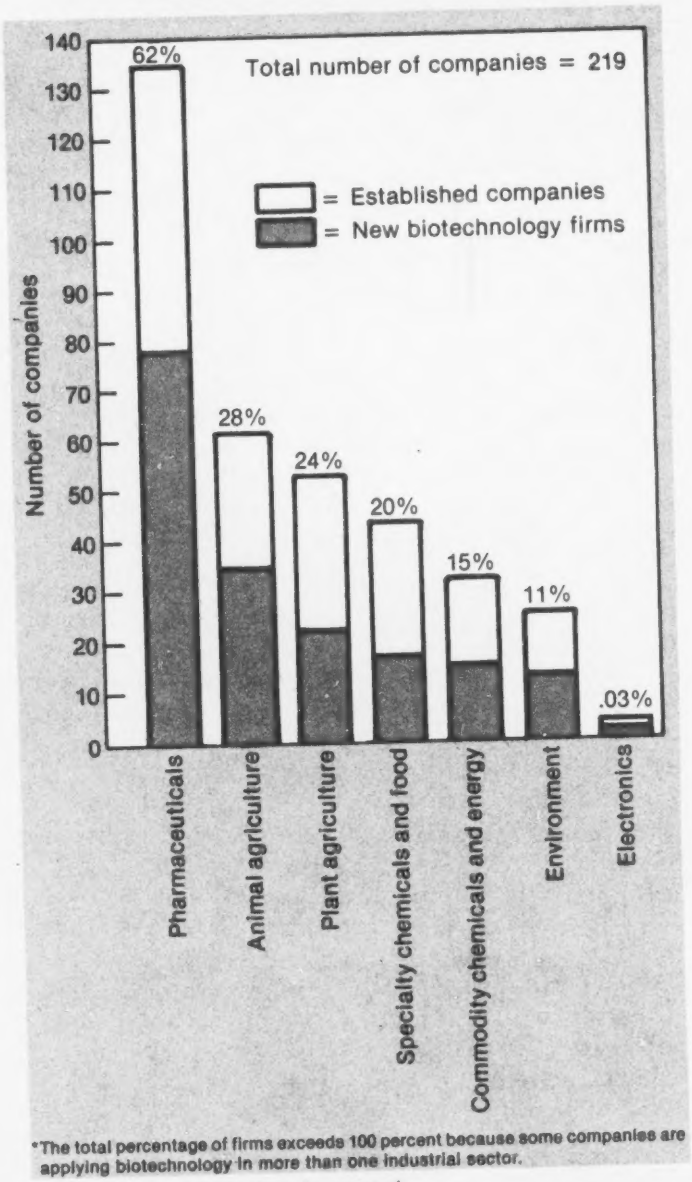
Figure 2.—The Relative Importance of Factors Affecting the Commercialization of Biotechnology


Government funding of basic and applied research
Financing and tax incentives for firms
Personnel availability and training
Antitrust law
Health, safety, and environmental regulation
Commercialization of biotechnology
Intellectual property law
International technology transfer, investment, and trade
University/industry relationships
Public perception
Targeting policies in biotechnology

SOURCE: Office of Technology Assessment.

Figure 3.—Percentage of Firms in the United States Pursuing Applications of Biotechnology in Specific Industrial Sectors*



*The total percentage of firms exceeds 100 percent because some companies are applying biotechnology in more than one industrial sector.

SOURCE: Office of Technology Assessment.

pansion of the U.S. research base, technology diffusion, and encouragement of technical advances through the increased domestic competition they create. The established companies, on the other hand, have assumed a major share of the responsibility for production and marketing of, and, when necessary, obtaining regulatory approval for, many of the earliest biotechnology products—the commercial stages where their resources are

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strongest. Recently, more and more established U.S. companies have been investing in their own research and production facilities, so the role of established companies in the U.S. biotechnology effort is expanding. Since established companies control the later stages of commercialization for many new products being developed through production and marketing agreements with NBFs, they will also have considerable control over the pace at which these new products reach the market. **Whether the dynamism arising from the competition and complementarity between NBFs and established companies will continue giving the United States a comparative advantage in product introduction remains unclear.** Some established companies, for example, might have disincentives to market new products that compete with products they already have on the market.

The commercial objectives of biotechnology R&D vary across national boundaries, as do the types of firms pursuing them. In the United States, commercial research projects appear primarily focused on pharmaceutical and plant and animal agriculture, and American competitive vigor in these application areas is correspondingly strong. Much of the investment in animal agriculture has been made by NBFs whereas much of the investment in plant agriculture has been made by major U.S. companies in agricultural chemicals and seed production.

In Japan, the Federal Republic of Germany, the United Kingdom, Switzerland, and France, biotechnology is being commercialized almost exclusively by established companies. **The Japanese consider biotechnology to be the last major technological revolution of this century, and the commercialization of biotechnology is accelerating over a broad range of industries, many of which have extensive bioprocessing experience.** The Japanese general chemical and petroleum companies especially are leaning strongly toward biotechnology, and some of them are making rapid advances in R&D through their efforts to make biotechnology a key technology for the future. Japanese companies have launched a competitive drive to enter international pharmaceutical markets. Furthermore, Japanese companies are world leaders in large-scale plant tissue culture, and the Ministry of International Trade and Industry has identified secondary compound synthesis from plants as a major area for commercialization. Unlike the United States, Japanese companies appear to be dedicating a great deal of biotechnology R&D to specialty chemical production, an area where they are already internationally prominent.

In Europe, large pharmaceutical and chemical companies, many of which already have significant strength in biologically produced product markets, are the major developers of biotechnology. The inherent financial, production, and marketing strengths of these companies will be important as the technology continues to emerge internationally. To the extent that large companies in Europe began their commercialization efforts later than U.S. companies and may also lack the dynamism and flexibility to compete with the combined efforts of NBFs and established companies in the United States, European companies could initially be at a competitive disadvantage. The United Kingdom's major pharmaceutical companies are among the leading

producers of biologically produced products, however, and their expertise in bioprocessing is impressive. Furthermore, the United Kingdom possesses some of the strongest basic research in interdisciplinary plant sciences. Whether or not the basic research will be commercialized successfully is difficult to predict.

U.S. competitive strength in biotechnology will be tested when large-scale production begins and bioprocessing problems are addressed. Pharmaceutical markets will be the first proving ground for U.S. competitive strength. The Japanese have extensive experience in bioprocess technology, and dozens of strong "old biotechnology" companies from several industrial sectors in Japan are using new biotechnology as a lever to enter profitable and expanding pharmaceutical markets. In addition to competing against Japanese companies, U.S. pharmaceutical and chemical companies will be competing against pharmaceutical and chemical companies of Western Europe, all of whom expect to recover their biotechnology investments through extensive international market penetration. There seem to be fewer European companies than Japanese companies strong in biotechnology now, but the competitive strength of European multinationals such as Hoechst (F.R.G.), Rhone Poulenc and Elf Aquitaine (France), ICI, Glaxo, and Wellcome (U.K.), and Hoffmann-La Roche (Switzerland) in the long run should not be underestimated.

Factors potentially important to international competitiveness in biotechnology

MOST IMPORTANT FACTORS

The three factors most important to the commercial development of biotechnology are financing and tax incentives for firms, government funding of basic and applied research, and personnel availability and training.

Financing and Tax Incentives for Firms.—The availability of venture capital to start new firms and tax incentives provided by the U.S. Government to encourage capital formation and stimulate R&D in the private sector are very important to the development of biotechnology in the United States. Since 1976, private venture capital in the United States has funded the startup of more than 100 NBFs. Many of these firms have already obtained second- and third-round financing, while others, still seeking additional funds, are relying heavily on the currently strong stock market, R&D limited partnerships, and private placements to fund research, production scale-up, clinical trials, and early product development. Between March and July of 1983, 23 NBFs raised about $450 million. R&D limited partnerships in biotechnology are expected to total $500 million in 1983 and $1.5 billion in 1984. Corporate equity investment in NBFs, although now diminishing, has also been an important source of financing for the new firms. From 1977 to August 1983, corporate venture capital supplied over $350 million to NBFs in equity investments alone.

The future performance of NBFs now extensively using the stock market and R&D limited partnerships for financing may influence the availability of financing for other firms seeking capital in the future. Most NBFs still

have negative earnings records. If some of these companies do not begin to manufacture soon in order to generate product revenues, investors may lose confidence in many of the firms' ability to commercialize biotechnology.

In the United States, venture capital is generally more difficult to obtain for later rounds of financing than for initial rounds, in part because venture capitalists are more eager to invest in earlier rounds to maximize their investment returns. The difficulty in getting subsequent financing for production scale-up may prove to be an insurmountable problem for some NBFs; the ability to self-finance may still be 5 to 10 years away.

Of all the six competitor countries, the United States has the most favorable tax environment for capital formation and small firm financing. Tax incentives, more than direct government funding, are used in the United States to stimulate business and encourage R&D expenditures. Thus, R&D limited partnerships, low capital gains tax rates, R&D tax credits (due to expire in 1985), and subchapter S provisions all benefit small firms.

In Japan and the European competitor countries, venture capital has played a very minor role in the commercialization of biotechnology, because these countries do not have tax provisions that promote the formation of venture capital and investment in high-risk ventures. As a consequence, few NBFs exist outside the United States. The established foreign companies that have initiated efforts to commercialize biotechnology can finance R&D activities through retained earnings. Established companies also have access to financing from bank loans. Additionally, the governments of Japan, the United Kingdom, the Federal Republic of Germany, and France have provided the private sector with public funds for biotechnology.

Tax incentives relevant to established companies commercializing biotechnology are those that stimulate R&D investments and those that encourage capital formation. Corporate tax rates are also important. For purposes of international comparisons, the most reliable basis is the overall effective corporate tax rate. Unlike statutory rates, the effective rate takes into account different definitions of taxable income and treatments of depreciation. Available studies suggest that Switzerland, followed by Japan and the United Kingdom, have the lowest effective corporate tax rates. The effective rates in the United States, the Federal Republic of Germany, and France are higher and about equal.

After the United States, Japan has the most financing available for companies using biotechnology. **The Japanese Government has made the commercialization of biotechnology a national priority and is financing cooperative interindustry biotechnology projects.** Most of the established companies commercializing biotechnology in Japan have at least one bank as a major shareholder that provides the company with low-interest loans for R&D. Wealthy individual investors in Japan, although few in number, have also provided some risk capital for new ventures.

Government Funding of Basic and Applied Research.—The objective of basic research is to gain a better understanding of the fundamental aspects of phenomena without goals toward the development of specific

products or processes. Such research, which is usually conducted by academic researchers who receive government funds, is critical to maintaining the science base on which a technology rests and to stimulating advances in a technology. The objective of applied research is to gain the knowledge needed to supply a recognized and specific need through a product or process. Such research is usually funded by industry. Generic applied science can be viewed as bridging a gap between basic science done mostly in universities and applied, proprietary science done in industry for the development of specific products. Such research is aimed at the solution of general problems that are associated with the use of a technology by industry. Generic applied research areas in biotechnology, for instance, include development of bioreactors, screening of micro-organisms for potential products, and better understanding of the genetics and biochemistry of industrially important micro-organisms. Support of basic science and of generic applied science is generally viewed as the responsibility of government, because it ultimately contributes to the public good and because it is high risk and too expensive for individual firms.

Of the competitor countries, the United States, both in absolute dollar amounts and in relative terms, has the largest commitment to basic research in biological sciences, although this commitment has decreased in the last few years. On the other hand, **the U.S. Government's commitment to generic applied research in areas such as bioprocess engineering and applied microbiology is relatively small.** In fiscal year 1983, the Federal Government spent $511 million on basic biotechnology research* compared to $6.4 million on generic applied research in biotechnology. Over the past several decades, the U.S. Government has decreased its commitment to generic applied research areas, while increasing its commitment to basic research. This policy has contributed to a widening scientific gap between purely basic research funded by the U.S. Government and short-term, relatively product-specific applied research funded by private industry. **The relatively low level of U.S. Government funding for generic applied research in biotechnology may cause a bottleneck in this country's biotechnology commercialization efforts.**

Like the United States, the Federal Republic of Germany, the United Kingdom, and Switzerland have a strong basic science base. Furthermore, the governments of Japan, the Federal Republic of Germany, and the United Kingdom fund a significant amount of generic applied science in biotechnology. Perhaps because Japan is able to rely on the United States and other countries to prove the early feasibility of new technologies for commercialization, the Japanese Government devotes more public funding to the solution of generic applied science problems than to basic research. This strategy worked well in the semiconductor industry, and Japan may very well attain a larger market share for biotechnology products than the United States because of its ability rapidly to apply results of basic research available from other countries.

*From $20 million to $30 million of the $511 million may actually be generic applied research, because definitions of biotechnology differ among agencies.

Personnel Availability and Training.—Adequately trained scientific and technical personnel are vital to any country's industrial competitiveness in biotechnology. For the most part, countries with good science funding in a field also have a good supply of well-trained people in that field.

The commercial development of biotechnology will require several specific types of technical personnel. Especially important categories include specialists in rDNA and MAb technology such as molecular biologists and immunologists; specialists in scale-up and downstream processing such as microbiologists, biochemists, and bioprocess engineers; and specialists for all aspects of biotechnology such as enzymologists and cell culture specialists. Scale-up personnel will become more important as companies using biotechnology move into production.

The United States currently has a competitive edge in the supply of molecular biologists and immunologists able to meet corporate needs, in part because the U.S. Government has provided substantial funding since World War II for basic life sciences research in U.S. universities. **The supply of Ph. D. plant molecular biologists and scale-up personnel in the United States, however, may be inadequate.** Like the United States, the United Kingdom and Switzerland have funded life sciences well and have a sufficient supply of basic biological scientists. Unlike the United States, Japan, the United Kingdom, and the Federal Republic of Germany maintained a steady supply of both industrial and government funding for generic applied microbiology and bioprocess engineering in the past few decades and have adequate personnel in these fields. In Japan and the Federal Republic of Germany, slight shortages of molecular biologists and immunologists exist; Japanese companies are seeking to train personnel abroad. France appears to have shortages in all types of personnel.

The training of personnel is important to the continuing commercialization of biotechnology. The United States has, for the most part, good training programs for basic scientists. Specialists in plant molecular biology may be in short supply now, but training in this discipline can be readily achieved with interdisciplinary programs in biology departments in universities. On the other hand, the United States does not have more than a handful of training programs for personnel in the more applied aspects of biotechnology, nor does it have Government programs, such as training grants, to support training in these fields. The training of bioprocess engineers and industrial microbiologists will require greater interdisciplinary cooperation between engineering and biology departments within universities.

The United States promotes and funds the training of foreign nationals in laboratories in the United States, yet funds very little training of Americans abroad. Foreign countries have many significant research programs in biotechnology that U.S. researchers could be visiting were funding available.

FACTORS OF MODERATE IMPORTANCE

The three factors found to be of moderate importance to international competitiveness in biotechnology are health, safety, and environmental regulation; intellectual property law; and university/industry relationships.

Health, Safety, and Environmental Regulation.—The only government controls directed specifically toward biotechnology are rDNA guidelines adopted by the six competitor countries.* Thus, OTA's analysis of the effect of health, safety, and environmental regulation on competitiveness in biotechnology focused on the drug laws for humans and animals and, to a lesser extent, on laws governing the production of chemicals and the deliberate release of novel organisms into the environment. Japan has the most stringent health and safety regulation for pharmaceuticals and animal drugs, followed by the United States. Switzerland appears to be the most liberal. Thus, **the regulatory environment favors the European companies over those of Japan and the United States reaching their own domestic markets sooner for pharmaceuticals and animal drugs.** In the United States, the Food and Drug Administration has taken the position that rDNA products whose active ingredients are identical to ones already approved or to natural substances will still need to go through the new product approval process. However, data requirements may be modified and abbreviated. This appears not to be the situation in the competitor countries, although there have not been definitive pronouncements by their regulatory agencies. **In all the competitor countries, there is some uncertainty as to the environmental regulation governing the deliberate release into the environment of genetically manipulated organisms.**

Intellectual Property Law.—The areas of intellectual property law most relevant to biotechnology are those dealing with patents, trade secrets, and plant breeders' rights. These areas work together as a system; an invention may be protected by one or more of them, and if one has disadvantages, a company can look to another. Thus, to the extent that a country's intellectual property law provides several alternative ways for companies to protect biotechnological inventions, it is more likely to be competitive in biotechnology.

In the final analysis, **the U.S. intellectual property system appears to offer the best protection for biotechnology of any system in the world,** thus providing the United States with a competitive advantage with regard to this factor. This advantage results from the fact that the system provides the widest choice of options for protecting biotechnological inventions, the broadest scope of coverage, and some of the best procedural safeguards. Some modifications and clarification of certain aspects of U.S. intellectual property law, however, might help U.S. competitiveness in biotechnology.

University/Industry Relationships.—University/industry interactions are a very effective way of tranferring technology from a research laboratory to industry. Such interactions promote communication between industrialists and academicians that benefits both sides.

Interest in the commercial potential of biotechnology has dramatically increased university/industry interactions, especially in the United States. Established U.S. and foreign companies have invested substantial amounts

*They are essentially voluntary and directed primarily at research. Their containment and oversight provisions have been substantially relaxed since they were originally adopted, and this trend is expected to continue. The United States has the most liberal guidelines, whereas Japan has the most stringent.

of money in U.S. universities doing work in biotechnology in order to gain a "window on the technology." **The various agreements in the United States appear to be working well, and fears concerning conflict of interest and commingling of Government and industry funds have diminished.**

Neither Japan nor the European competitor countries identified in this assessment have as many or as well-funded university/industry relationships as the United States does, but varying degrees of cooperation do exist. In Japan, the ties between university applied research departments and industry have always been close. Additionally, the Japanese Government is implementing new policies to encourage closer ties between basic research scientists and industry. In the Federal Republic of Germany, the Federal Ministry of Science and Technology (BMFT, Bundesministerium für Forschung und Technologie) has a history of promoting close contact between academia and industry and is cosponsoring with industry many projects important to biotechnology. Switzerland encourages communication between individuals in academia and industry, and relationships are easy to maintain. The universities in both the United Kingdom and France have had very few ties with industry in biotechnology, but the governments of both countries have recently set up programs designed to encourage university/industry relationships.

LEAST IMPORTANT FACTORS

The least important of the 10 factors analyzed were found to be antitrust law; international technology transfer, investment, and trade; government targeting policies in biotechnology; and public perception. Any of these factors, however, could become important as the technology develops and products reach the marketplace.

Antitrust Law.—The antitrust laws of the United States and the other major competitors in biotechnology are generally similar in that they prohibit restraint of trade and monopolization. However, the foreign laws generally provide for exemptions and vest much discretion with the enforcement authorities, especially in Japan. Thus, in practice, they are often less restrictive than in the United States. In addition, countries differ in the consequences to firms for failure to comply with antitrust laws. In the United States, the consequences of noncompliance can be more severe than in the competitor countries because private, in addition to Government, suits can be brought against alleged antitrust violators, and treble damages are assessed if a violation is found.

U.S. companies commercializing biotechnology face no major antitrust compliance problems, because the lack of concentration and the absence of measurable markets mean that most types of joint research arrangements would not be anticompetitive. Technology licensing agreements can raise antitrust concerns, but these generally are not unique to biotechnology. However, there is some degree of uncertainty about the scope and applicability of the antitrust laws to R&D joint ventures and licensing agreements. This uncertainty, plus the expense of litigation and

the threat of treble damages, could deter some activities that might lead to innovation in biotechnology, thus limiting the ability of U.S. companies commercializing biotechnology to exploit their technology.* For these reasons, the current U.S. antitrust laws may have some modest adverse effect on biotechnology.

International Technology Transfer, Investment, and Trade.—Technology transfer across national boundaries can be promoted or inhibited by export control laws and by laws governing international joint ventures and technology licensing. **U.S. export control laws, which are the most restrictive of the competitor countries, may have a slightly adverse effect on the competitiveness of U.S. companies commercializing biotechnology because they could cause delays that result in the loss of sales to foreign competitors.** Furthermore, these laws may need clarification as biotechnology products proceed to the marketplace because there is some uncertainty as to what products or data will be restricted.

Foreign exchange and investment control laws help prevent access to domestic markets and technology by foreign firms. The United States has the fewest controls, whereas Japan and France have the most control mechanisms. Thus, **U.S. markets are the most accessible to foreign firms and therefore the most vulnerable to foreign competition,** whereas Japanese and French markets are the least accessible and the most protected against foreign competition.

Trade policy is not important to the commercialization of biotechnology today because of the small number of products that have reached the market and because trade in biotechnologically produced products is not likely to raise any unique trade issues. However, trade policy will become increasingly important as more products reach the marketplace, especially in the area of pharmaceuticals, where significant nontariff barriers, such as conforming to country standards with appropriate testing data, quality control standards, and packaging requirements exist.

Government Targeting Policies in Biotechnology.—The governments of four of the competitor countries—Japan, the Federal Republic of Germany, the United Kingdom, and France—have instituted comprehensive programs to help domestic companies develop certain areas of biotechnology. Though targeting policies are not of great importance when compared to other competitive factors, they could tip the balance of a competitive position in the future.

Public Perception.—As a factor influencing competitiveness, public perception of the risks and benefits of biotechnology is probably of greater importance in the United States than in the other competitor countries. Historically, the American public has been more involved than the public in Japan or the European countries with issues pertaining to genetic research and technology (e.g., issues regarding the safety of rDNA research).

*In addition, the rigid application of certain "per se rules" in the area of licensing may actually lead to anticompetitive results.

In all of the countries, the effect of public perception as a factor influencing competitiveness will be greatly increased in the event of an accident or perceived negative consequence of biotechnology.

Other influences on competitiveness in biotechnology

Three other considerations that should be noted in evaluating competitive positions in the commercialization of biotechnology are, for each country, historical patterns of industrial commercialization, the availability of natural resources, and cultural attitudes toward risk-taking.

Historically, some countries have moved research results into commercialization rapidly, more rapidly than others. This observation is especially important in this analysis of biotechnology. For instance, the United Kingdom has a good science base, trained personnel, and industries that could be using these new technologies; however, the United Kingdom may not be a major contender in the commercialization of biotechnology mainly because it does not have a history of rapid commercialization. On the other hand, both the United States and Japan historically commercialize scientific advances rapidly.

The absence or presence of certain natural resources may also determine how quickly a country moves into the commercialization of biotechnology. For instance, Japan does not have domestic petroleum resources. Because biomass can potentially replace petroleum as a feedstock in the chemical industry, Japan may be more interested in applying biotechnology in the chemical industry than a country, such as the United Kingdom, which has domestic petroleum resources. The United States, a country that produces excesses of grain each year, may find commercialization of processes that can use grain as a feedstock particularly attractive. However, it is too early to predict the degree to which natural resources will determine the commercial applications of biotechnology a country may undertake.

The United States, as a general rule, is not averse to risk-taking in business. Risk-taking is a part of the American lifestyle. European countries are more risk averse. Since investment in biotechnology is considered risky, countries that are more risk averse are less likely to move rapidly to commercialize biotechnology.

Conclusion

The unique complementarities between established and new firms, the well-developed science base, the availability of finances, and an entrepreneurial spirit have been important in giving the United States its present competitive advantage in the commercialization of biotechnology. In order to maintain this advantage, increased funding of research and training of personnel in basic and generic applied sciences, especially bioprocess engineering and industrial microbiology, may be necessary. The United States may also need to be concerned with the continued availability of finances

for NBFs until they are self-supporting. On most of the other factors influencing competitiveness, the United States rates very favorably, although there are changes in laws and policies that could potentially improve or help maintain the U.S. competitive position. These changes include clarification and modification of particular aspects of intellectual property law; health, safety, and environmental regulation; antitrust law; and export control law.

Japan will be the most serious competitor of the United States in the commercialization of biotechnology. Japan has a very strong bioprocess technology base on which to build, and the Japanese Government has specified biotechnology as a national priority. The demonstrated ability of the Japanese to commercialize developments in technology rapidly will surely manifest itself in biotechnology.

The Federal Republic of Germany, the United Kingdom, Switzerland, and France lag behind the United States and Japan in the commercialization of biotechnology. The European countries generally do not promote risk-taking, either industrially or in their government policies. Additionally, they have many fewer companies commercializing biotechnology. Thus, **the European countries are not expected to be as strong general competitors in biotechnology as the United States and Japan.** In markets for specific products, including some pharmaceuticals, specialty chemicals, and animal agriculture products, however, some European companies will undoubtedly be strong international competitors.

Issues and options

To improve the competitive position of the United States, legislation could be directed toward any of the 10 factors OTA identified as influencing competitiveness, although coordinated legislation directed toward all of the factors might be more effective in promoting U.S. biotechnology efforts. Chapters in this report discuss options that are specific to the development of biotechnology. Some of the options presented are limited and straightforward, such as some options concerning health and safety regulation and R&D limited partnerships. Other options are much broader with potentially large political, ethical, and financial considerations. Some examples of the latter include establishing university/industry cooperative research centers, regulating the deliberate release of genetically manipulated organisms into the environment, and changing patterns of research funding. Clearly, the adoption of some options may occur more rapidly than the adoption of others.

Policy options in some areas are not specific to biotechnology but apply to high technology or industry in general. These options are to:

- improve U.S. science and engineering education and the retraining of industrial personnel,
- change U.S. antitrust law to promote more research collaboration among domestic firms,

- regulate imports into the United States to protect domestic industries,
- regulate the transfer of technology from the United States to other countries, and
- target specific industries or technologies for Federal assistance.

There are many arguments for and against these options that are beyond the scope of this report. Because of their broad applicability to industry in general, these options are not discussed in this report. It is important to note, however, that legislation in any of these areas could affect the development of biotechnology and potentially have a large influence on the U.S. competitive position.

NOTE: Copies of the full report, "Commercial Biotechnology: An International Analysis," can be purchased from the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402, GPO stock No. 052-003-00939-1.

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